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(54) Title: ANTIFUNGAL NAIL COMPOSITION AND METHOD OF USE

(57) Abstract: The invention is a method for treating onychomycosis in humans comprising contacting a fungal infected nail with a composition comprising an effective amount of a copper salt. Most preferably, the fungal infected nail is treated with 10 % (weight/weight) aqueous copper(II)sulfate. Treating human nails with the copper salt composition can be used to detect fungal infection before routine physical symptoms are presented. Fungal infection is also prevented by pre-treatment of nails with the copper salt composition.

ANTIFUNGAL NAIL COMPOSITION AND METHOD OF USE

TECHNICAL FIELD OF THE INVENTION

This invention relates to a composition for treating fungal-infected human nails.

BACKGROUND

Nail fungal infections (also known as onychomycosis, tinea unguium, or ringworm of the nail; hereinafter referred to as "onychomycosis") are caused by a fungal invasion of the keratinous structure of a fingernail or toe nail by a variety of fungi including *Trychophyton* sp., *Microsporum* sp., *Epidermaphyton* sp.; *Candida* sp., *Trichosporon* sp., *Geotrichum* sp., *Scopulariopsis* sp., *Aspergillus* sp., *Acremonium* sp., *Fusarium* sp., *Phyllosticta* sp., *Hendersonula* sp., and *Cheatomium* sp. A fungal infected nail typically has a yellowish color that starts at one corner of the nail and spreads towards the cuticle. Over time, the infected nail presents as a thickened, lusterless, discolored nail, often with keratotic debris accumulated under the tip. Left untreated, the infected nail plate often becomes brittle, flaking, crumbling, friable, striated, deformed, separated, or completely destroyed. While onychomycosis is generally not painful, the unsightly appearance of the infected nail can be a source of embarrassment for most patients. For diabetics or immunosuppressed patients, an infected nail left untreated can result in severe infection.

Various systemic and topical preparations have been used to treat onychomycosis. Generally, the course of treatment is long-term and accompanied by a high relapse rate. Itraconazole, which inhibits the cytochrome P-450-dependent synthesis of ergosterol, a vital component of fungal cell membranes, is available for oral administration. The recommended course of treatment with itraconazole for an infected toe nail is twelve weeks. For an infected fingernail, two one-week pulses of orally administered itraconazole separated by three weeks is recommended. Griseofulvin is an oral preparation that binds newly formed keratin, thus making new nail tissue resistant to fungal infection. Recommended treatment involves trimming away infected nail tissue as the nail grows out and requires at least four months of treatment for an infected fingernail

and at least 6 months for an infected toe nail. Because griseofulvin is derived from *Penicillium*, the possibility of cross-sensitivity with penicillin exists, limiting its use to individuals not allergic to penicillins. Terbinafine hydrochloride is an oral preparation that prevents fungal growth by inhibiting squalene epoxidase and blocking fungal cell
5 membrane synthesis. Recommended treatment of terbinafine hydrochloride is six weeks for an infected fingernail and 12 weeks for an infected toe nail. Topical antifungal agents include imidazoles or triazoles such as clotrimazole and ketoconazole, ciclopirox, amphotericin-B, gentian violet, resorcinol, and iodine. Despite the current availability of antifungal agents for treating onychomycosis, new compositions that are less expensive
10 to administer with a minimal relapse rate are desired.

The antifungal use of various copper salts is well known in the area of agriculture and aquaculture. For example, copper sulfate, copper carbonate, copper oxychloride, copper ammonium complex, copper oxide, copper hydroxide, copper naphthenates, and copper quinolinates have all been reported as effective fungicidal agents. The antifungal
15 properties of copper sulfate solutions have been known for over 230 years and were utilized to eliminate wheat bunt (*Tilletia* sp.) and potato blight, the cause of the Irish Potato Famine. The oldest of the treatments to prevent the growth of *Phytophthora infestans*, the causative agent in potato blight, are known as the Bordeaux mixture and the Burgundy mixture. Both solutions are prepared for spraying on potato plants to prevent
20 blight according to a rigorous schedule synchronized to the fungus lifecycle. A 2% Bordeaux mixture is most commonly used for potatoes and consists of a 2:1 mixture of copper sulfate and hydrated lime in 100 gallons of water. A 1% Burgundy mixture consists of a 4:5 mixture of copper sulfate and sodium bicarbonate in 40 gallons of water. Despite the availability of synthetic antifungal agents to prevent potato blight, organic
25 farmers still utilize the Bordeaux mixture and the Burgundy mixture because they are safe, inexpensive, and easy to use.

In U.S. Patent No. 4,822,595 issued April 18, 1989, Corliss, et al. disclose a hoof lotion that contains linseed oil as a dispersing agent, lanolin as a moisturizer, turpentine as a drying agent, iodine as an antiseptic agent, pine tar as a sticking agent, hydrogen
30 peroxide as an antibacterial agent and copper sulfate as a fungicidal agent. Copper

sulfate is 0.53% by weight of the hoof lotion. Corliss, et al. described the utility of the claimed hoof lotion as killing and preventing fungal growths and healing cracks, brittle surfaces and hoof dryness.

Undecylenic acid as well as its copper, calcium and zinc salts and combinations thereof have been reported as antifungal agents for use in the treatment of athlete's foot (tinea pedis). However, the foot creams, sprays, and ointments containing undecylenates have been limited to the treatment of skin fungal infections and specifically disclaimed as treatment for fungal nail infections.

A method for treating human onychomycosis has now been found comprising contacting fungal infected human nails with copper salts, preferably copper sulfate.

SUMMARY OF THE INVENTION

In one aspect, the invention is a nail composition comprising an effective antifungal amount of a copper salt effective for arresting fungal invasion in human nail tissue. Exemplary copper salts useful in the composition of the present invention include copper acetates, copper ammonium complexes, copper carbonates, copper perchlorates, copper halides, copper gluconates, copper oxyhalides, copper lactates, copper naphthenates, copper oxides, copper quinolates, copper salicylates, copper selenates, copper sulfates, and copper tartrates. Preferably, the copper salt is copper(II)sulfate. The composition preferably comprises from 1% (weight/weight) to 32% (weight/weight) aqueous copper(II)sulfate; more preferably, 10% (weight/weight) aqueous copper(II)sulfate. Preferably, the composition is selected from the group consisting of a nail polish, acrylic nail product, gel nail product, cuticle softening solution, nail conditioning formulation, artificial nail product, and nail ornamental product. In one embodiment, the composition is a nail polish. In another embodiment, the nail composition further comprises a fixative. In another embodiment, the nail composition further comprises an adhesive. In one embodiment, the composition is a cuticle softening solution. The composition can also release the copper salt over time using a controlled-release formulation.

In one aspect, the invention is a nail composition comprising an effective antifungal amount of a copper salt effective for arresting fungal growth on human nail tissue. Exemplary copper salts useful in the composition of the present invention include copper acetates, copper ammonium complexes, copper carbonates, copper perchlorates, copper halides, copper gluconates, copper oxyhalides, copper lactates, copper naphthenates, copper oxides, copper quinolines copper salicylates, copper selenates, copper sulfates, and copper tartrates. Preferably, the copper salt is copper(II)sulfate. The composition preferably comprises from 1% (weight/weight) to 32% (weight/weight) aqueous copper(II)sulfate; more preferably, 10% (weight/weight) aqueous copper(II)sulfate. Preferably, the composition is selected from the group consisting of a nail polish, acrylic nail product, gel nail product, cuticle softening solution, nail conditioning formulation, artificial nail product, and nail ornamental product. In one embodiment, the composition is a nail polish. In another embodiment, the nail composition further comprises a fixative. In another embodiment, the nail composition further comprises an adhesive. In one embodiment, the composition is a cuticle softening or nail conditioning solution. The composition can also release the copper salt over time using a controlled-release formulation.

In another aspect, the present invention is use of a copper salt in the manufacture of an antifungal nail medicament comprising an effective antifungal amount of said copper salt effective for arresting fungal invasion in human nail tissue.

In another aspect, the present invention is use of a copper salt in the manufacture of an antifungal nail medicament comprising an effective antifungal amount of said copper salt effective for arresting fungal growth on human nail tissue.

In another aspect, the present invention is use of a copper salt in the manufacture of a medicament for detecting fungal infection in a human nail comprising an effective antifungal amount of said copper salt to stain fungal infected human nail tissue

In another aspect, the present invention is use of a copper salt in the manufacture of a medicament for preventing fungal infection in a healthy human nail comprising an effective antifungal amount of said copper salt.

In another aspect, the present invention is use of a copper salt in the manufacture of a medicament for preventing fungal growth on a healthy human nail comprising an effective antifungal amount of said copper salt.

5 In another aspect, the invention is a method for treating a fungal infection of a human nail comprising topically applying an effective antifungal amount of a composition comprising a copper salt to the nail, wherein the effective amount arrests fungal invasion of nail tissue. Preferably, the method utilizes one or more of the nail compositions disclosed herein.

10 In another aspect, the invention is a method for treating a fungal growth on a human nail comprising topically applying an effective antifungal amount of a composition comprising a copper salt to the nail, wherein the effective amount arrests fungal growth. Preferably, the method utilizes one or more of the nail compositions disclosed herein.

15 In another aspect, the invention is a method for persistent treatment of a fungal infection of a human nail comprising topically applying an effective antifungal amount of a composition comprising a copper salt to the nail, wherein the effective amount capable of arresting fungal invasion of nail tissue persists on the fungal infected nail tissue after repeated washing of the nail with a suitable solvent. Preferably, the method utilizes one or more of the nail compositions disclosed herein.

20 In another aspect, the invention is a method of detecting fungal infection in a human nail comprising topically applying an effective amount of a composition comprising a copper salt to the infected nail, wherein the composition visibly stains any fungal infected nail tissue; washing the infected nail with a suitable solvent to remove stain from uninfected nail tissue; and equating the persistent stained nail tissue with
25 fungal infected nail tissue. Preferably, the method utilizes one or more of the nail compositions disclosed herein.

In another aspect, the invention is a method of monitoring fungal infection in a human nail comprising, at a first time point, topically applying an effective amount of a composition comprising a copper salt to the infected nail, wherein the composition

visibly stains any fungal infected nail tissue; washing the nail with a suitable solvent to remove stain from uninfected nail tissue; equating the persistent stained nail tissue with fungal infected nail tissue; comparing the area of persistent stained nail tissue to the area of unstained nail tissue; at a second time point, topically applying an effective amount of

5 a composition comprising a copper salt to the nail, wherein the composition stains any fungal infected nail tissue; washing the nail with a suitable solvent to remove stain from uninfected nail tissue; equating the persistent stained nail tissue with fungal infected nail tissue; comparing the area of persistent stained nail tissue to the area of unstained nail tissue; wherein an increase in the area ratio of unstained nail tissue to persistent stained

10 nail tissue at said second time point to the area ratio of unstained nail tissue to persistent stained nail tissue at said first time point indicates a decrease in fungal infection.

Preferably, the method utilizes one or more of the nail compositions disclosed herein.

In another aspect, the invention is a method of preventing fungal infection in a healthy human nail comprising topically applying an effective antifungal amount of a

15 composition comprising a copper salt to the nail, wherein the composition persists on the healthy nail after repeated washing of the nail with a suitable solvent. Preferably, the method utilizes one or more of the nail compositions disclosed herein.

In another aspect, the invention is a method of preventing fungal growth on a healthy human nail comprising topically applying an effective antifungal amount of a

20 composition comprising a copper salt to the nail, wherein the composition persists on the healthy nail after repeated washing of the nail with a suitable solvent. Preferably, the method utilizes one or more of the nail compositions disclosed herein.

DETAILED DESCRIPTION

In one aspect, the present invention is a composition for treating human

25 onychomycosis comprising an effective antifungal amount of at least one copper salt, such as copper sulfate, which is safe for topical application to human nail tissue and an acceptable carrier. Upon application of the composition of the present invention to fungal infected human nail tissue, the fungal matter embedded in the infected nail is contacted with an effective antifungal amount of the copper salt(s). In one embodiment

of the present invention, it is advantageous that the composition of the present invention be reapplied to human nail tissue after an extended period of time. In another embodiment, the composition of the present invention remains in contact with the nail for an extended period of time.

5 Exemplary copper salts include but are not limited to copper acetates, copper ammonium complexes, copper carbonates, copper perchlorates, copper halides, copper gluconates, copper oxyhalides, copper lactates, copper naphthenates, copper oxides, copper quinolinates copper salicylates, copper selenates, copper sulfates, and copper tartrates can be used. Preferably, the copper salt is copper sulfate, also known in the art
10 as copper sulfate, cupric sulfate, copper(II)sulfate, Roman vitriol, Fehling solution A, salzburg vitriol, sulfuric acid copper(2+) salt, blue copper, copper monosulfate, CuSO_4 , copper(2+)sulfate, cupric sulfate anhydrous, incracide E 51, blue stone, hi-chel, blue vitriol, natural chalcantite, and other names. The most preferred form of copper sulfate utilized in the present invention is copper(II)sulfate pentahydrate. The copper salts useful
15 in the present invention are commercially available from general chemical suppliers such as Sigma Chemical Company (St. Louis, MO), Aldrich (Milwaukee, WI), and Mallinckrodt Laboratory Chemicals (Phillipsburg, NJ). It is understood that the present invention can utilize copper salts having a wide range of purity, including but not limited to industrial, technical, or reagent grade, provided that any impurity present in the copper
20 salt is not harmful to humans on topical application.

For most uses, the composition of present invention preferably comprises an amount of one or more copper salts equivalent to the amount of copper found in a 1-32% (weight/weight) aqueous composition of copper (II) sulfate at room temperature. However, practical concentrations can vary from trace amounts to a paste of
25 approximately 100% (weight/weight) of copper salts such as copper sulfate, depending upon the frequency of application, type of application, type of carrier used, and toxicity and/or patient sensitivity to the copper salt as disclosed herein. The preferred concentration of copper salts useful in the present invention can vary depending upon the type of application, wherein the concentration of copper salt in a composition for the
30 treatment of fungal infection is preferably higher than the concentration of copper salt

used in nail polish or adhesive. Moreover, the preferred concentration of copper salt useful in the present invention for the treatment of fungal infection can vary depending upon the preferred treatment regimen. For example, a stronger concentration of copper salt is preferable in a composition which is infrequently applied; however, for a patient
5 having sensitivity to copper salt, a composition with a lower concentration of copper salt applied more frequently would be preferred. For the treatment of fungal infection, a preferred composition of the present invention comprises copper (II)sulfate at a final concentration of about 1%-32% (weight/weight); preferably, 7%-20% (weight/weight); most preferably, 10% (weight/weight) at room temperature.

10 An acceptable carrier useful in the composition of the present invention is any solvent system which stably solubilizes the copper salt and is tolerated by human tissue. An acceptable carrier must solubilize the copper salt(s) and prevent subsequent recrystallization of the copper salt(s) over time. Any carrier suitable for the active ingredient of the current invention is herein considered part of this application. The
15 cosmetic arts are rich in chemicals suitable for applying to human skin and nails. The following compounds are merely examples and not meant to be limiting in any way. Carriers that may be used in conjunction with copper salts include moisturizers such as dimethicone silicone, isopropyl lanolate, lanolin, oleic acid, panthenol, and stearic acid. Surfactants or detergents such as sodium laureth sulfate can be added to the copper salt
20 composition of the present invention to provide foaming, cleansing, wetting, emulsifying, solubilizing, and dispersing properties to the solution. Preservatives that may be used in a copper salt composition may include tocopherol and EDTA. Additionally, antimicrobials such as parabens, quaternium-15, methylisothiazolinone, DMDM hydantoin, and phenoxyethanol may also be used in a copper salt formulation. It may be
25 advantageous to include thickeners, like microcrystalline waxes, polyethylene thickeners, and carbomer thickeners, in a copper salt composition. Solvents that may be included in a copper salt formulation include water, a combination of water and glycerol, and a combination of water and a volatile organic solvent(s), including but not limited to butylene and propylene glycol, cyclomethicone, and glycerin. Emulsifiers such as
30 glyceryl monostearate, lauramide DEA, and polysorbates, may be advantageous to add to

a copper salt composition. To increase the penetration of the copper salt composition into the fungal infected nail, penetrating agents can optionally be added. It is to be well understood that any person skilled in the art could choose appropriate surfactant, penetrating, moisturizing, antimicrobial, and emulsifying agents if desired to modify the copper salt composition, all of which are contemplated by the present invention.

For treatment of fungal infection, an effective antifungal amount of copper salt(s) can also be added to existing nail products such as a commercially available nail polish (e.g., REVLON, New York, New York; L'Oreal USA, Inc., New York, New York, and CoverGirl, Procter & Gamble, Cincinnati, Ohio), acrylic nail products, gel nail products, cuticle softening solutions, nail conditioning preparations, or various products used in association with artificial nails or ornamentals. By adding a fixative, the copper salt composition can be applied as a semi-permanent film to the nails prior to the application of nail polish, artificial nails or ornamentals. Applying the composition of the present invention in a nail polish or as a film applied to the nails prior to the application of nail polish, artificial nails or ornamentals provides the advantage of having the copper salt-containing product remaining in contact with the nail for an extended period of time. Also, the nail polish can optionally comprise pigment when it is advantageous to minimize the appearance of staining of nail tissue caused by the copper salt. It is contemplated that one product or a combination of products comprising copper salt in an effective antifungal amount can be used.

The present invention is a method for treating onychomycosis in humans comprising applying a copper salt composition, preferably with an absorbent swab, felt, gauze, eyedropper or brush, to the fungal infected nail. Preferably, the copper salt composition is applied for approximately 30 minutes and allowed to air dry. On drying, a powder coating of copper salt covers the treated skin and nail. On washing with water or other suitable solvent, the porous (infected) portion of the nail may be permanently stained from the copper salt, while normal nail tissue and skin is temporarily stained and returns to normal coloration. A suitable solvent for washing is any solvent which is capable of solubilizing the copper salt without causing damage to the nail tissue or surrounding skin. The washing solvent and the carrier in the copper salt composition can

be the same or different. For copper (II) sulfate, water is a preferred solvent for washing. Repeated washing of hands or feet over time generally results in further migration of the copper salt into the infected nail. Thus, normal washing does not interrupt the treatment process or require repeated application of the copper salt solution after each washing. As
5 the treated nail grows, a narrow band having a reddish pink color may appear immediately behind the blue-stained infected nail portion. As new, healthy nail tissue appears, the stained infected portion of the nail grows beyond the nail bed and is trimmed away. Application of the copper salt composition is repeated upon fading of the stain, more preferably at least once monthly until signs of infection are eliminated.

10 In addition to the copper salt treatment of the present invention, the method to treat onychomycosis in humans can include processes that are generally part of nail health maintenance including trimming and sanding the nail, keeping the nail dry, and treating the affected areas with chemicals to enhance the absorption of and/or prevent the leaching out of the copper salt from the nail over time. For example, clear or colored nail
15 polish can be applied to the copper salt treated nail. Likewise, stained, treated nails can be cosmetically disguised by the application of colored nail polish.

Another aspect to the method of using a copper salt composition to treat human onychomycosis includes treating nails before they present the symptoms of onychomycosis. For example, if one toe nail exhibits the symptoms of onychomycosis,
20 all toe nails can be treated even if symptoms are not yet apparent. Furthermore, since the copper salt composition will stain only the nail portions exhibiting fungal invasion, the progress of the fungal infection within one nail can be monitored, or possible spreading to other nails can be detected. For example, a staining copper salt, preferably copper sulfate, can be added to routine soaking solutions used in the art prior to manicuring or
25 pedicuring.

The copper salt composition of the present invention can also be used to prevent onychomycosis as well as the growth of noninvasive fungi residing on the surface of human nails, for example, fungi commonly seen in association with the use of artificial nails or ornamentals. In one aspect, a copper salt can be added to nail polish
30 formulations, acrylic nail products, gel nail products, cuticle softening solutions, nail

conditioning preparations, or various products used in association with artificial nails or
ornamentals to effectively prevent the growth of fungi residing on the nail. By adding a
fixative, the copper salt composition can be applied as a semi-permanent film to the nails
prior to the application of nail polish, artificial nails or ornamentals. Preferably, the
5 copper salt can be applied in a time-release formulation. It is contemplated that one
product or a combination of products comprising copper salt can be used in the
prevention of onychomycosis or superficial fungal growth.

Because of the potential staining properties of the copper salt composition of the
present invention, containment of the copper salt composition during shipping and
10 storage as well as upon application to infected nails is preferable. One preferred method
is a waterproof paper, plastic or foil package containing an absorbent swab or felt or
gauze pad saturated with copper salt composition, whereupon tearing away a portion of
the package exposes the copper salt composition saturated absorbent tip of the swab or a
portion of the copper salt composition saturated felt or gauze pad which can be directly
15 applied to the infected nail. In another preferred method, the copper salt composition is
encapsulated in a breakable ampule, the breakable ampule is enclosed in a plyable
container capable of confining the ampule upon breakage and having one sealed end and
one opened end that is packed with an absorbent material, and the whole device is
enclosed in a waterproof paper, plastic or foil package. On use, the ampule is broken to
20 release the copper salt composition, the absorbent material is saturated with the copper
salt composition, a portion of the package is torn away to expose the copper salt
composition saturated absorbent material which can be directly applied to the infected
nail.

Example 1: Toe Nail Treatment

25 A male patient diagnosed as having a fungal infected toe nail, began treatment by
applying an aqueous 10% (w/v) copper(II)sulfate pentahydrate solution to the infected
nail using a copper sulfate saturated gauze pad. The copper sulfate solution was applied
to the infected toe nail for approximately thirty minutes and then allowed to air dry.
Excess copper sulfate powder was removed by washing two times with water. The
30 infected portion of the patient's nail had a bluish color. As the treated nail grew, healthy

nail tissue appeared at the base of the nail bed while the infected portion of the nail was pushed off the nail bed and periodically trimmed away. Over time, the fungal infection did not spread to healthy nail tissue and the stained, treated portion of the nail was removed.

5

Example 2: Toe Nail Treatment

A male patient diagnosed as having a fungal infected toe nail began treatment by applying with a cotton swab an aqueous 10% (w/v) copper(II)sulfate pentahydrate solution to the infected nail as well as to all nails on the same foot. The copper sulfate solution was applied to his toe nails for approximately thirty minutes and then allowed to
10 air dry. Excess copper sulfate powder was removed by washing two-three times with water. The patient's infected nail had a bluish color where the infection was present. All other nails return to normal coloration, indicating that the fungal infection had not spread from the infected toe to neighboring toe nails on the same foot. As the treated nail grew, healthy nail tissue appeared at the base of the nail bed while the infected portion of the
15 nail was pushed off the nail bed and periodically trimmed away. Monthly, the copper sulfate solution was applied as given above to the infected nail and to all nails on the same foot. The infected portion of the patient's nail continued to have a bluish color. All other nails returned to normal coloration on washing, indicating that the fungal infection still had not spread from the infected toe to neighboring toe nails on the same foot. Over
20 time, the fungal infection did not spread to healthy nail tissue and the stained, treated portion of the nail was removed, resulting in a normal healthy nail.

Example 3: Fingernail Treatment

A female patient diagnosed as having a fungal infected fingernail began treatment by applying with a cotton swab an aqueous 10% (w/v) copper(II)sulfate pentahydrate
25 solution to the infected nail as well as to all nails on the same hand. The copper sulfate solution was applied to her fingernails for approximately thirty minutes and then allowed to air dry. Excess copper sulfate powder was removed by washing two-three times with water. The patient's infected nail had a bluish color where the infection was present. All other nails returned to normal coloration, indicating that the fungal infection had not
30 spread from the infected fingernail to neighboring fingernails on the same hand. The

patient routinely covered her fingernails in an opaque, colored nail enamel which completely disguised the infected nail. As the treated nail grew, healthy nail tissue appeared at the base of the nail bed while the infected portion of the nail was pushed off the nail bed and periodically trimmed away. Monthly, the copper sulfate solution was applied as given above to the infected fingernail and to all fingernails on the same hand. The infected portion of the patient's nail continued to have a bluish color. All other nails returned to normal coloration on washing, indicating that the fungal infection still had not spread from the infected fingernail to neighboring fingernails on the same hand. Over time, the fungal infection did not spread to healthy nail tissue and the stained, treated portion of the nail was removed, resulting in a normal healthy nail.

Example 4: Fingernail Treatment

A female, 30 years old, was diagnosed as having an infection of onychomycosis of the right index fingernail. The nail was separating from the nail bed along the right side of the nail and along the cuticle, leaving the nail hinged along the left side of the nail only. The patient required a bandage to prevent the nail from tearing free. The right side of the nail displayed the characteristic yellowing and rough, thick texture associated with the fungal infection. Prior to the first treatment on Day 1, all fingernail polish was removed from the nail using over-the-counter nail polish remover. A bandage was soaked with a preparation consisting of a 10% aqueous copper sulfate solution with a trace of detergent added to act as a surfactant. The bandage was applied to the infected nail and secured in place. Care was given to ensure that the solution soaked into the crevice along the edge of the nail bed and cuticle. Subsequent hand washing provided additional wetting which drove more of the copper sulfate solution into the nail bed and surrounding crevice. The bandage was worn for two days and then replaced with a clean dry bandage to protect the nail from snagging. The treatment was repeated on Day 31 and again on Day 45; no further treatments were given. Between treatments, the patient was permitted to resume the use of fingernail polish between treatments. On Day 132, the nail was examined. The patient was no longer wearing a dry bandage to protect the nail. New pink nail growth was present from the cuticle to a point midway along the nail. The new portion of the nail was attached normally on both sides of the nail from the

- cuticle to the midpoint. There was a slight “keloid type” ridge across the nail at the midpoint. The old fungal infected nail was still separated from the midpoint of the right side of the nail to the end of the nail. The new growth immediately behind the “keloid type” ridge was rough in texture, typical of nail regrowth following a fungal infection.
- 5 However, the nail newly emerging from the cuticle was smoother, like an uninfected nail.

- It is to be understood that the above description is of preferred exemplary embodiments of the invention and is intended to be illustrative of the invention, but is not to be construed to limit the scope of the invention in any way. Modifications may be made in the composition features of the invention without departing from the scope of the
- 10 invention. It will be readily apparent to those skilled in the art that alternative materials may also be utilized without departing from the scope of the invention.

I claim:

1. A nail composition comprising an antifungal amount of a copper salt effective for arresting fungal growth in human nail tissue.
2. The composition of Claim 1, wherein said copper salt is selected from the group consisting of copper acetates, copper ammonium complexes, copper carbonates, copper perchlorates, copper halides, copper gluconates, copper oxyhalides, copper lactates, copper naphthenates, copper oxides, copper quinolines, copper salicylates, copper selenates, copper sulfates, and copper tartrates.
3. The composition of Claim 1, wherein said copper salt is copper(II)sulfate.
4. The composition of Claim 3, wherein said composition comprises from 1% (weight/weight) to 32% (weight/weight) aqueous copper(II)sulfate.
5. The composition of Claim 3, wherein said composition comprises 10% (weight/weight) aqueous copper(II)sulfate.
6. The composition of Claim 1, 2, 3, 4 or 5, wherein said composition is selected from the group consisting of a nail polish, acrylic nail product, gel nail product, cuticle softening solution, nail conditioning formulation, artificial nail product, and nail ornamental product.
7. The composition of Claim 1, 2, 3, 4 or 5, wherein said composition is a nail polish.
8. The composition of Claim 1, 2, 3, 4 or 5, wherein said composition is a cuticle softening solution.
9. The composition of Claim 1, 2, 3, 4 or 5, wherein said composition further comprises a fixative.
10. The composition of Claim 1, 2, 3, 4 or 5, wherein said composition further comprises an adhesive.
11. The composition of Claim 1, 2, 3, 4 or 5, wherein said copper salt is released over time using a controlled-release formulation.
12. The composition of Claim 6, wherein said copper salt is released over time using a controlled-release formulation.

13. The composition of Claim 7, wherein said copper salt is released over time using a controlled-release formulation.

14. The composition of Claim 8, wherein said copper salt is released over time using a controlled-release formulation.

15. The composition of Claim 9, wherein said copper salt is released over time using a controlled-release formulation.

16. The composition of Claim 10, wherein said copper salt is released over time using a controlled-release formulation.

17. A nail composition comprising an antifungal amount of a copper salt effective for arresting fungal growth on human nail tissue.

18. The composition of Claim 17, wherein said copper salt is selected from the group consisting of copper acetates, copper ammonium complexes, copper carbonates, copper perchlorates, copper halides, copper gluconates, copper oxyhalides, copper lactates, copper naphthenates, copper oxides, copper quinolines, copper salicylates, copper selenates, copper sulfates, and copper tartrates.

19. The composition of Claim 17, wherein said copper salt is copper(II)sulfate.

20. The composition of Claim 19, wherein said composition comprises from 1% (weight/weight) to 32% (weight/weight) aqueous copper(II)sulfate.

21. The composition of Claim 19, wherein said composition comprises 10% (weight/weight) aqueous copper(II)sulfate.

22. The composition of Claim 17, 18, 19, 20 or 21, wherein said composition is selected from the group consisting of a nail polish, acrylic nail product, gel nail product, cuticle softening solution, nail conditioning formulation, artificial nail product, and nail ornamental product.

23. The composition of Claim 17, 18, 19, 20 or 21, wherein said composition is a nail polish.

24. The composition of Claim 17, 18, 19, 20 or 21, wherein said composition is a cuticle softening solution.

25. The composition of Claim 17, 18, 19, 20 or 21, wherein said composition further comprises a fixative.

26. The composition of Claim 17, 18, 19, 20 or 21, wherein said composition further comprises an adhesive.

27. The composition of Claim 17, 18, 19, 20 or 21, wherein said copper salt is released over time using a controlled-release formulation.

28. The composition of Claim 22, wherein said copper salt is released over time using a controlled-release formulation.

29. The composition of Claim 23, wherein said copper salt is released over time using a controlled-release formulation.

30. The composition of Claim 24, wherein said copper salt is released over time using a controlled-release formulation.

31. The composition of Claim 25, wherein said copper salt is released over time using a controlled-release formulation.

32. The composition of Claim 26, wherein said copper salt is released over time using a controlled-release formulation.

33. Use of a copper salt in the manufacture of an antifungal nail medicament comprising an effective antifungal amount of said copper salt effective for arresting fungal growth in human nail tissue.

34. Use of a copper salt in the manufacture of an antifungal nail medicament comprising an effective antifungal amount of said copper salt effective for arresting fungal growth on human nail tissue.

35. Use of a copper salt in the manufacture of a medicament for detecting fungal infection in a human nail comprising an effective amount of said copper salt to stain fungal infected human nail tissue

36. Use of a copper salt in the manufacture of a medicament for preventing fungal infection in a healthy human nail comprising an effective antifungal amount of said copper salt.

37. Use of a copper salt in the manufacture of a medicament for preventing fungal growth on a healthy human nail comprising an effective antifungal amount of said copper salt.

38. The use of Claim 33, 34, 35, 36 or 37, wherein said composition is according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32.

39. A method for treating a fungal infection in human nail tissue comprising topically applying an effective antifungal amount of a composition comprising a copper salt to said nail tissue, wherein said effective amount arrests fungal invasion in said nail tissue.

40. A method for treating fungal growth on a human nail comprising topically applying an effective antifungal amount of a composition comprising a copper salt to said nail, wherein said effective amount arrests fungal growth.

41. A method for persistent treatment of a fungal infection of human nail tissue comprising topically applying an effective antifungal amount of a composition comprising a copper salt to said nail tissue, wherein said effective amount capable of arresting fungal invasion of said nail tissue persists on said fungal infected nail tissue
5 after repeated washing of said nail tissue with a suitable solvent.

42. A method for detecting fungal infection in a human nail comprising
a. topically applying an effective amount of a composition comprising a copper salt to said nail, wherein said composition visibly stains any fungal infected nail tissue;
b. washing said nail with a suitable solvent to remove stain from uninfected nail
5 tissue; and
c. equating the persistently stained nail tissue with fungal infected nail tissue.

43. A method of monitoring fungal infection in a human nail comprising
a. at a first time point, topically applying an effective amount of a composition comprising a copper salt to said nail, wherein said composition visibly stains any fungal infected nail tissue;
5 b. washing said nail with a suitable solvent to remove stain from uninfected nail tissue;

- c. equating the persistently stained nail tissue with fungal infected nail tissue;
- d. comparing the area of persistently stained nail tissue to the area of unstained nail tissue
- 10 e. at a second time point, topically applying an effective amount of a composition comprising a copper salt to said nail, wherein said composition stains any fungal infected nail tissue;
- f. washing said nail with a suitable solvent to remove stain from uninfected nail tissue;
- 15 g. equating the persistently stained nail tissue with fungal infected nail tissue;
- h. comparing the area of persistently stained nail tissue to the area of unstained nail tissue;
- wherein an increase in the area ratio of unstained nail tissue to persistently stained nail tissue at said second time point to the area ratio of unstained nail tissue to
- 20 persistently stained nail tissue at said first time point indicates a decrease in fungal infection.

44. A method of preventing fungal infection in a healthy human nail comprising topically applying an effective antifungal amount of a composition comprising a copper salt to said nail, wherein said composition persists on said healthy nail after repeated washing of said nail with a suitable solvent.

45. A method of preventing fungal growth on a healthy human nail comprising topically applying an effective antifungal amount of a composition comprising a copper salt to said nail, wherein said composition persists on said healthy nail after repeated washing of said nail with a suitable solvent.

46. The method of Claim 39, 40, 41, 42, 43, 44 or 45, wherein said composition is according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/29438

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/04 A61K33/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. M. BUTLER ET AL : "The use of phenanthroline metal chelates for the control of topical infections due to bacteria, fungi and protozoa" MEDICAL JOURNAL OF AUSTRALIA., vol. 2, 1970, pages 309-314, XP008001374 page 311, right-hand column, line 5 -page 312, right-hand column, last paragraph ---	1, 33-46
X	DATABASE WPI Section Ch, Week 199714 Derwent Publications Ltd., London, GB; Class D21, AN 1997-152592 XP002193016 & RU 2 063 744 C (FITOLON CO LTD), 20 July 1996 (1996-07-20) abstract --- -/--	1, 33-46

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 198630 Derwent Publications Ltd., London, GB; Class D21, AN 1986-195058 XP002193017 & RO 88 114 A (INTR PROD COSMETICE MIRAJ), 30 December 1985 (1985-12-30) abstract ---	1-3, 33-46
X	WO 98 52927 A (SCIVOLETTO ROSEMARIE) 26 November 1998 (1998-11-26) page 4, line 16 - line 27; claims 27,28,35 ---	1,33-46
X	WO 93 11735 A (AQUANAUTICS CORP) 24 June 1993 (1993-06-24) page 12, line 13 - line 25; claims 1,15,28-32 ---	1-3, 33-46
X	US 3 257 280 A (ARON RICHTER) 21 June 1966 (1966-06-21) claims 1-3,9 ---	1,33-46
X	US 4 933 175 A (PASSARELLI MICHAEL A) 12 June 1990 (1990-06-12) claims 1,4 ---	1,33-46
A	US 4 822 595 A (CORLISS LYAL S ET AL) 18 April 1989 (1989-04-18) cited in the application claim 1 -----	1-3

INTERNATIONAL SEARCH REPORT

Intern I Application No
PCT/US 01/29438

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
RU 2063744	C	20-07-1996	RU 2063744 C1	20-07-1996
RO 88114	A	30-12-1985	RO 88114 A2	30-12-1985
WO 9852927	A	26-11-1998	AU 7582398 A WO 9852927 A1	11-12-1998 26-11-1998
WO 9311735	A	24-06-1993	AU 3328693 A WO 9311735 A1 US 5422366 A	19-07-1993 24-06-1993 06-06-1995
US 3257280	A	21-06-1966	NONE	
US 4933175	A	12-06-1990	NONE	
US 4822595	A	18-04-1989	NONE	

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